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(74) Agents: CIAMPORCERO, Audley, A., Jr. et al.; Johnson & Johnson, One Johnson & Johnson Plaza, New Brunswick, NJ 08933-7003 (US).

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(54) Title: ANTICONVULSANT DERIVATIVES USEFUL IN TREATING PSORIASIS

(57) Abstract

Anticonvulsant derivatives useful in treating psoriasis are disclosed.

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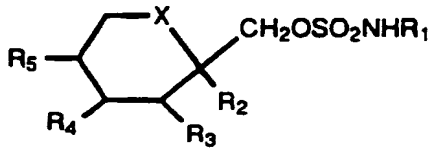
ANTICONVULSANT DERIVATIVES USEFUL IN TREATING PSORIASIS

BACKGROUND OF THE INVENTION

Compounds of Formula I:



are structurally novel antiepileptic compounds that are highly effective anticonvulsants in animal tests (Maryanoff, B.E, Nortey, S.O., Gardocki, J.F., Shank, R.P. and Dodgson, S.P. *J. Med. Chem. 30*, 880-887, 1987; Maryanoff, B.E., Costanzo, M.J., Shank, R.P., Schupsky, J.J., Ortegon, M.E., and Vaught J.L. Bioorganic & Medicinal Chemistry Letters 3, 2653-2656, 1993, McComsey, D.F. and Maryanoff, B.E., J. Org. Chem. 1995). These compounds are covered by US Patent No. 4,513,006. One of these compounds 2,3:4,5-bis-O-(1-methylethylidene)-ß-D-fructopyranose sulfamate known as topiramate has been demonstrated in clinical trials of human epilepsy to be effective as adjunctive therapy or as monotherapy in treating simple and complex partial seizures and secondarily generalized seizures (E. FAUGHT, B.J. WILDER, R.E. RAMSEY, R.A. REIFE, L D. KRAMER, G.W. PLEDGER, R.M. KARIM et. al., Epilepsia 36 (S4) 33, 1995; S.K. SACHDEO, R.C. SACHDEO, R.A. REIFE, P. LIM and G. PLEDGER, Epilepsia 36 (S4) 33, 1995), and is currently marketed for the treatment of simple and complex partial seizure epilepsy with or without secondary generalized seizures in Great Britain, Finland, the United States and Sweden and applications for regulatory approval are presently pending in numerous countries throughout the world.

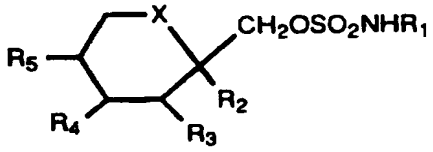
Compounds of Formula I were initially found to possess anticonvulsant activity in the traditional maximal electroshock seizure (MES) test in mice

(SHANK, R.P., GARDOCKI, J.F., VAUGHT, J.L., DAVIS, C.B., SCHUPSKY, J.J., RAFFA, R.B., DODGSON, S.J., NORTEY, S.O., and MARYANOFF, B.E., Epilepsia 35 450-460, 1994). Subsequent studies revealed that Compounds of Formula I were also highly effective in the MES test in rats. More recently topiramate was found to effectively block seizures in several rodent models of epilepsy (J. NAKAMURA, S. TAMURA, T. KANDA, A. ISHII, K. ISHIHARA, T. SERIKAWA, J. YAMADA, and M. SASA, Eur. J. Pharmacol. 254 83-89, 1994), and in an animal model of kindled epilepsy (A. WAUQUIER and S. ZHOU, Epilepsy Res. 24, 73-77, 1996).

Recent preclinical studies on topiramate have revealed previously unrecognized pharmacological properties which suggest that topiramate should be effective in treating some other disorders. One of these is psoriasis.

DISCLOSURE OF THE INVENTION

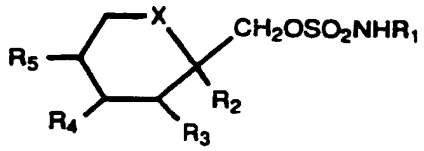
Accordingly, it has been found that compounds of the following formula I:



wherein X is O or CH_2, and R_1, R_2, R_3, R_4 and R_5 are as defined hereinafter are useful in treating psoriasis.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The sulfamates of the invention are of the following formula (I):

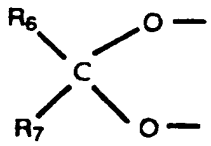


wherein

X is CH_2 or oxygen;

R_1 is hydrogen or alkyl; and

R_2, R_3, R_4 and R_5 are independently hydrogen or lower alkoxy, when X is oxygen, R_2 and R_3 and/or R_4 and R_5 together may be a methylenedioxy group of the following formula (II):



wherein

R_6 and R_7 are the same or different and are hydrogen, lower alkyl or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring.

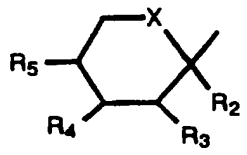
R_1 in particular is hydrogen or alkyl of about 1 to 4 carbons, such as methyl, ethyl and iso-propyl. Alkyl throughout this specification includes straight and branched chain alkyl. Alkyl groups for R_2, R_3, R_4, R_5, R_6 and R_7 are of about 1 to 3 carbons and include methyl, ethyl, iso-propyl and n-propyl.

A particular group of compounds of formula (I) are those wherein X is oxygen and both R_2 and R_3, and R_4 and R_5 together are methylenedioxy groups of the formula (II), wherein R_6 and R_7 are both hydrogen, both alkyl, or combine to form a spiro cyclopentyl or cyclohexyl ring, in particular where R_6 and R_7 are both alkyl such as methyl. A second group of compounds are those wherein X is CH_2 and R_4 and R_5 are joined to form a benzene ring. A third

group of compounds of formula (I) are those wherein both R_2 and R_3 are hydrogen.

The compounds of formula (I) may be synthesized by the following methods:

(a) Reaction of an alcohol of the formula RCH_2OH with a chlorosulfamate of the formula $ClSO_2NH_2$ or $ClSO_2NHR_1$ in the presence of a base such as potassium a-butoxide or sodium hydride at a temperature of about -20° to 25° C and in a solvent such as toluene, THF or dimethylformamide wherein R is a moiety of the following formula (III):



(b) Reaction of an alcohol of the formula RCH_2OH with sulfurylchloride of the formula SO_2Cl_2 in the presence of a base such as triethylamine or pyridine at a temperature of about -40° to 25° C in a solvent such as diethyl ether or methylene chloride to produce a chlorosulfate of the formula RCH_2OSO_2Cl.

The chlorosulfate of the formula RCH_2OSO_2Cl may then be reacted with an amine of the formula R_1NH_2 at a temperature of abut 40° to 25° C in a solvent such as methylene chloride or acetonitrile to produce a compound of formula (I). The reaction conditions for (b) are also described by T. Tsuchiya et al. in Tet. Letters, No. 36, p. 3365 to 3368 (1978).

(c) Reaction of the chlorosulfate RCH_2OSO_2Cl with a metal azide such as sodium azide in a solvent such as methylene chloride or acetonitrile yields an azidosulfate of the formula $RCH_2OSO_2N_3$ as described by M.

Hedayatullah in Tet. Lett. p. 2455-2458 (1975). The azidosulfate is then reduced to a compound of formula (I) wherein R_1 is hydrogen by catalytic hydrogenation, e.g. with a noble metal and H_2 or by heating with copper metal in a solvent such as methanol.

The starting materials of the formula RCH_2OH may be obtained commercially or as known in the art. For example, starting materials of the formula RCH_2OH wherein both R_2 and R_3, and R_4 and R_5 are identical and are of the formula (II) may be obtained by the method of R. F. Brady in Carbohydrate Research, Vol. 14, p. 35 to 40 (1970) or by reaction of the trimethylsilyl enol ether of a R_6COR_7 ketone or aldehyde with fructose at a temperature of about 25° C, in a solvent such a halocarbon, e.g. methylene chloride in the presence of a protic acid such as hydrochloric acid or a Lewis Acid such as zinc chloride. The trimethylsilyl enol ether reaction is described by G. L. Larson et al in J. Org. Chem. Vol. 38, No. 22, p. 3935 (1973).

Further, carboxylic acids and aldehydes of the formulae RCOOH and RCHO may be reduced to compounds of the formula RCH_2OH by standard reduction techniques, e.g. reaction with lithium aluminum hydride, sodium borohydride or borane-THF complex in an inert solvent such a diglyme, THF or toluene at a temperature of about 0° to 100° C, e.g. as described by H.O. House in "Modern Synthetic Reactions", 2nd Ed., pages 45 to 144 (1972).

The compounds of formula I: may also be made by the process disclosed US Patent: No.4,513,006, which is incorporated by reference herein.

The compounds of formula I include the various individual isomers as well as the racemates thereof, e.g., the various alpha and beta attachments, i.e., below and above the plane of the drawing, of R_2, R_3, R_4 and R_5 on the 6-membered ring. Preferably, the oxygens of the methylenedioxy group (II) are attached on the same side of the 6-membered ring.

The activity of the compounds of formula I in treating psoriasis was first evidenced in clinical studies conducted to evaluate the efficacy of topiramate in treating epilepsy. At least three patients who coincidentally had psoriasis reported that there was a marked reduction in the psoriatic lesions. Therefore, preclinical in vitro studies were conducted to evaluate the effects of topiramate on keratinocyte function as a putative mechanism of action for its potential beneficial effects in treating psoriasis. One of the hallmarks of psoriatic lesions is hyperproliferative epidermal keratinocytes. In general, agents that affect the proliferation of keratinocytes have an inverse effect on differentiation, i.e. they would inhibit growth and enhance differentiation. Two measures of keratinocyte function were therefore evaluated: cell growth and differentiation.

In these studies, keratinocytes were grown in Medium154, a low calcium medium supplemented with bovine pituitary extract (BPE), bovine insulin, bovine transferrin, human epidermal growth factor (EGF) and hydrocortisone. Keratinocytes were grown to 60-80% confluence and subcultured by using trypsin/EDTA.

Four separate experiments were performed to evaluate the dose-dependent effect of topiramate on keratinocyte cell growth as measured by maturity after six days of treatment. Topiramate was dissolved in DMSO to make a 100 mM stock solution. In all experiments the final concentration of DMSO in the cell incubation medium was 0.1%. Vehicle controls (0.1% DMSO) were included in each experiment. Cell growth was induced by a combination of the growth factors EGF and BPE. Topiramate had a modest inhibitory effect on cell growth under these assay conditions; however, no dose dependence was observed (R.W Johnson Pharmaceutical Research Institute Laboratory Notebook No. 12183 and 12540). The maximal response was observed at 10 micromolar, 32 ± 10% inhibition. While there was a trend toward inhibition of cell growth, this did not reach statistical significance ($p>0.05$).

The effect of topiramate on keratinocyte differentiation was measured by the expression of transglutaminase-1 protein after three days of treatment. Three separate experim nts were performed. Differentiation was evaluated in both low calcium and high calcium incubation conditions. An increase in differentiation would be most readily observed under low calcium conditions whereas an inhibition of differentiation could be detected under conditions of high calcium-induced differentiation. Topiramate caused a modest increase in transglutaminase-1 protein with both conditions, indicating an enhancing effect. A follow-up study was conducted which extended the incubation time to 5 days to look for further enhancement. No additional increases in transglutaminase-1 were observed in this latter study.

The results of these studies indicate that topiramate's effects on keratinocyte function are consistent with those expected for an agent that would affect the hyperproliferative keratinocyte response associated with psoriasis; inhibition of cell growth and enhancement of differentiation.

For treating psoriasis, a compound of formula (I) may be employed at a daily dosage in the range of about 50 to 400 mg administered orally, usually in two divided doses, for an average adult human. A unit dose would contain about 25 to 200 mg of the active ingredient. Alternatively, a compound of formula (I) may be administered topically to the affected area of the skin once or twice daily at a dosage in the range of 5 to 50 mg.

To prepare the pharmaceutical compositions of this invention, one or more sulfamate compounds of formula (I) are intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral, by suppository, or parenteral. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. Thus, for liquid oral preparations, such as for example, suspensions, elixirs and solutions, suitable carriers and

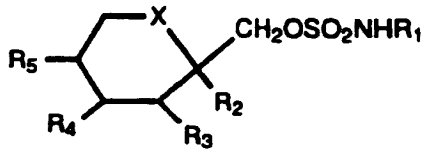
additives include water, glycols, oils, alcohols, flav ring agents, preservatives, coloring agents and the like; for solid oral preparations such as, for example, powders, capsules and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar coated or enteric coated by standard techniques. Suppositories may be prepared, in which case cocoa butter could be used as the carrier. For parenterals, the carrier will usually comprise sterile water, though other ingredients, for example, for purposes such as aiding solubility or for preservation, may be included. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed.

Topiramate is currently available for oral administration in round tablets containing 25 mg, 100 mg or 200 mg of active agent. The tablets contain the following inactive ingredients: lactose hydrous, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, purified water, carnauba wax, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, synthetic iron oxide, and polysorbate 80.

The pharmaceutical compositions herein will contain, per dosage unit, e.g., tablet, capsule, powder injection, teaspoonful, suppository and the like from about 25 to about 200 mg of the active ingredient.

WHAT IS CLAIMED IS:

1. A method for treating psoriasis comprising administering to a human afflicted with such condition a therapeutically effective amount for treating such condition of a compound of the formula I:

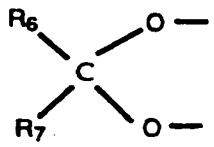


wherein

X is CH_2 or oxygen;

R_1 is hydrogen or alkyl; and

R_2, R_3, R_4 and R_5 are independently hydrogen or lower alkyl and, when X is CH_2, R_4 and R_5 may be alkene groups joined to form a benzene ring and, when X is oxygen, R_2 and R_3 and/or R_4 and R_5 together may be a methylenedioxy group of the following formula (II):



wherein

R_6 and R_7 are the same or different and are hydrogen, lower alkyl or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring.

2. The method of claim 1 wherein the compound of formula I is topiramate.

3. The method of claim 1, wherein the therapeutically effective amount is of from about 50 to 400 mg.

4. The method of claim 1, wherein the amount is of from about 25 to 200 mg.

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INTERNATIONAL SEARCH REPORT

International Application No PCT/US 97/10891

A. CLASSIFICATION OF SUBJECT MATTER

A 61 K 31/35, A 61 K 31/36

According to International Patent Classification (IPC) or to both national classification and IPC 6

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A 61 K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4513006 A (MARYANOFF, B.E. et al.) 23 April 1985 (23.04.85), abstract, claims 5-9, column 1, lines 16-33, column 3, line 15 - column 5, line 19, example 3 (cited in the application). --	1-4
A	US 4792569 A (MARYANOFF, B.E. et al.) 20 December 1988 (20.12.88), abstract, claims 1,10-12, column 1, lines 20-37, column 3, line 29 - column 4, line 33. ----	1,3,4

☐ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search
14 November 1997

Date of mailing of the international search report
16.12.97

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte onal application No.
PCT/US 97/ 10891

Box I Obs rvati ns where ertain claims were f und unsearchabl (Continuati n f item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 1-4
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANHANG

zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

ANNEX

to the International Search Report to the International Patent Application No.

ANNEXE

au rapport de recherche international relatif à la demande de brevet international n°

PCT/US 97/10891 SAE 168598

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The Office is in no way liable for these particulars which are given merely for the purpose of information.

La présente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche international visée ci-dessus. Les renseignements fournis sont donnés à titre indicatif et n'engagent pas la responsibilité de l'Office.

Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
US A 4513006	23-04-85	AT E 36149	15-08-88
		AU A1 33504/84	04-04-85
		AU B2 564842	27-08-87
		CA A1 1241951	13-09-88
		DE C0 3473143	08-09-88
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		DK A 1981/91	09-12-91
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		DK C 165004	08-02-93
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		EP A3 138441	27-08-86
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		HU B 194540	29-02-88
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		NO C 170280	30-09-92
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		ZA A 8407550	28-05-86
		US A 4582916	15-04-86
US A 4792569	20-12-88	keine - none - rien	

CORRECTED VERSION*

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(74) Agents: CIAMPORCERO, Audley, A., Jr. et al.; Johnson & Johnson, One Johnson & Johnson Plaza, New Brunswick, NJ 08933-7003 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

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(54) Title: ANTICONVULSANT DERIVATIVES USEFUL IN TREATING PSORIASIS

(57) Abstract

Anticonvulsant derivatives useful in treating psoriasis are disclosed.

*(Referred to in PCT Gazette No. 28/1998, Section II)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
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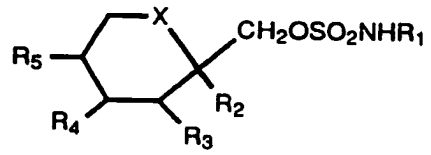
EE	Estonia	LR	Liberia	SG	Singapore		

ANTICONVULSANT DERIVATIVES USEFUL IN TREATING PSORIASIS

BACKGROUND OF THE INVENTION

Compounds of Formula I:



are structurally novel antiepileptic compounds that are highly effective anticonvulsants in animal tests (Maryanoff, B.E, Nortey, S.O., Gardocki, J.F., Shank, R.P. and Dodgson, S.P. *J. Med. Chem. 30*, 880-887, 1987; Maryanoff, B.E., Costanzo, M.J., Shank, R.P., Schupsky, J.J., Ortegon, M.E., and Vaught J.L. Bioorganic & Medicinal Chemistry Letters 3, 2653-2656, 1993, McComsey, D.F. and Maryanoff, B.E., J. Org. Chem. 1995). These compounds are covered by US Patent No. 4,513,006. One of these compounds 2,3:4,5-bis-O-(1-methylethylidene)-ß-D-fructopyranose sulfamate known as topiramate has been demonstrated in clinical trials of human epilepsy to be effective as adjunctive therapy or as monotherapy in treating simple and complex partial seizures and secondarily generalized seizures (E. FAUGHT, B.J. WILDER, R.E. RAMSEY, R.A. REIFE, L D. KRAMER, G.W. PLEDGER, R.M. KARIM et. al., Epilepsia 36 (S4) 33, 1995; S.K. SACHDEO, R.C. SACHDEO, R.A. REIFE, P. LIM and G. PLEDGER, Epilepsia 36 (S4) 33, 1995), and is currently marketed for the treatment of simple and complex partial seizure epilepsy with or without secondary generalized seizures in Great Britain, Finland, the United States and Sweden and applications for regulatory approval are presently pending in numerous countries throughout the world.

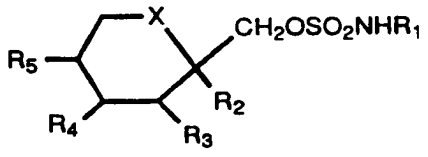
Compounds of Formula I were initially found to possess anticonvulsant activity in the traditional maximal electroshock seizure (MES) test in mice

(SHANK, R.P., GARDOCKI, J.F., VAUGHT, J.L., DAVIS, C.B., SCHUPSKY, J.J., RAFFA, R.B., DODGSON, S.J., NORTEY, S.O., and MARYANOFF, B.E., Epilepsia 35 450-460, 1994). Subsequent studies revealed that Compounds of Formula I were also highly effective in the MES test in rats. More recently topiramate was found to effectively block seizures in several rodent models of epilepsy (J. NAKAMURA, S. TAMURA, T. KANDA, A. ISHII, K. ISHIHARA, T. SERIKAWA, J. YAMADA, and M. SASA, Eur. J. Pharmacol. 254 83-89, 1994), and in an animal model of kindled epilepsy (A. WAUQUIER and S. ZHOU, Epilepsy Res. 24, 73-77, 1996).

Recent preclinical studies on topiramate have revealed previously unrecognized pharmacological properties which suggest that topiramate should be effective in treating some other disorders. One of these is psoriasis.

DISCLOSURE OF THE INVENTION

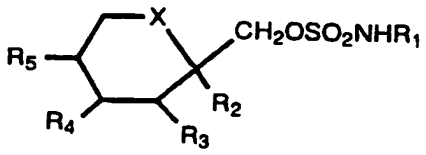
Accordingly, it has been found that compounds of the following formula I:



wherein X is O or CH_2, and R_1, R_2, R_3, R_4 and R_5 are as defined hereinafter are useful in treating psoriasis.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The sulfamates of the invention are of the following formula (I):

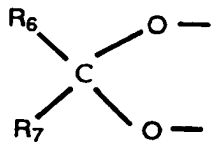


wherein

X is CH_2 or oxygen;

R_1 is hydrogen or alkyl; and

R_2, R_3, R_4 and R_5 are independently hydrogen or lower alkoxy, when X is oxygen, R_2 and R_3 and/or R_4 and R_5 together may be a methylenedioxy group of the following formula (II):



wherein

R_6 and R_7 are the same or different and are hydrogen, lower alkyl or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring.

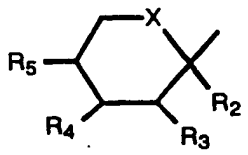
R_1 in particular is hydrogen or alkyl of about 1 to 4 carbons, such as methyl, ethyl and iso-propyl. Alkyl throughout this specification includes straight and branched chain alkyl. Alkyl groups for R_2, R_3, R_4, R_5, R_6 and R_7 are of about 1 to 3 carbons and include methyl, ethyl, iso-propyl and n-propyl.

A particular group of compounds of formula (I) are those wherein X is oxygen and both R_2 and R_3, and R_4 and R_5 together are methylenedioxy groups of the formula (II), wherein R_6 and R_7 are both hydrogen, both alkyl, or combine to form a spiro cyclopentyl or cyclohexyl ring, in particular where R_6 and R_7 are both alkyl such as methyl. A second group of compounds are those wherein X is CH_2 and R_4 and R_5 are joined to form a benzene ring. A third

group of compounds of formula (I) are those wherein both R_2 and R_3 are hydrogen.

The compounds of formula (I) may be synthesized by the following methods:

(a) Reaction of an alcohol of the formula RCH_2OH with a chlorosulfamate of the formula $ClSO_2NH_2$ or $ClSO_2NHR_1$ in the presence of a base such as potassium a-butoxide or sodium hydride at a temperature of about -20° to 25° C and in a solvent such as toluene, THF or dimethylformamide wherein R is a moiety of the following formula (III):



(b) Reaction of an alcohol of the formula RCH_2OH with sulfurylchloride of the formula SO_2Cl_2 in the presence of a base such as triethylamine or pyridine at a temperature of about -40° to 25° C in a solvent such as diethyl ether or methylene chloride to produce a chlorosulfate of the formula RCH_2OSO_2Cl.

The chlorosulfate of the formula RCH_2OSO_2Cl may then be reacted with an amine of the formula R_1NH_2 at a temperature of abut 40° to 25° C in a solvent such as methylene chloride or acetonitrile to produce a compound of formula (I). The reaction conditions for (b) are also described by T. Tsuchiya et al. in Tet. Letters, No. 36, p. 3365 to 3368 (1978).

(c) Reaction of the chlorosulfate RCH_2OSO_2Cl with a metal azide such as sodium azide in a solvent such as methylene chloride or acetonitrile yields an azidosulfate of the formula $RCH_2OSO_2N_3$ as described by M.

Hedayatullah in Tet. Lett. p. 2455-2458 (1975). The azidosulfate is then reduced to a compound of formula (I) wherein R_1 is hydrogen by catalytic hydrogenation, e.g. with a noble metal and H_2 or by heating with copper metal in a solvent such as methanol.

The starting materials of the formula RCH_2OH may be obtained commercially or as known in the art. For example, starting materials of the formula RCH_2OH wherein both R_2 and R_3, and R_4 and R_5 are identical and are of the formula (II) may be obtained by the method of R. F. Brady in Carbohydrate Research, Vol. 14, p. 35 to 40 (1970) or by reaction of the trimethylsilyl enol ether of a R_6COR_7 ketone or aldehyde with fructose at a temperature of about 25° C, in a solvent such a halocarbon, e.g. methylene chloride in the presence of a protic acid such as hydrochloric acid or a Lewis Acid such as zinc chloride. The trimethylsilyl enol ether reaction is described by G. L. Larson et al in J. Org. Chem. Vol. 38, No. 22, p. 3935 (1973).

Further, carboxylic acids and aldehydes of the formulae RCOOH and RCHO may be reduced to compounds of the formula RCH_2OH by standard reduction techniques, e.g. reaction with lithium aluminum hydride, sodium borohydride or borane-THF complex in an inert solvent such a diglyme, THF or toluene at a temperature of about 0° to 100° C, e.g. as described by H.O. House in "Modern Synthetic Reactions", 2nd Ed., pages 45 to 144 (1972).

The compounds of formula I: may also be made by the process disclosed US Patent: No.4,513,006, which is incorporated by reference herein.

The compounds of formula I include the various individual isomers as well as the racemates thereof, e.g., the various alpha and beta attachments, i.e., below and above the plane of the drawing, of R_2, R_3, R_4 and R_5 on the 6-membered ring. Preferably, the oxygens of the methylenedioxy group (II) are attached on the same side of the 6-membered ring.

The activity of the compounds of formula I in treating psoriasis was first evidenced in clinical studies conducted to evaluate the efficacy of topiramate in treating epilepsy. At least three patients who coincidentally had psoriasis reported that there was a marked reduction in the psoriatic lesions. Therefore, preclinical in vitro studies were conducted to evaluate the effects of topiramate on keratinocyte function as a putative mechanism of action for its potential beneficial effects in treating psoriasis. One of the hallmarks of psoriatic lesions is hyperproliferative epidermal keratinocytes. In general, agents that affect the proliferation of keratinocytes have an inverse effect on differentiation, i.e. they would inhibit growth and enhance differentiation. Two measures of keratinocyte function were therefore evaluated: cell growth and differentiation.

In these studies, keratinocytes were grown in Medium154, a low calcium medium supplemented with bovine pituitary extract (BPE), bovine insulin, bovine transferrin, human epidermal growth factor (EGF) and hydrocortisone. Keratinocytes were grown to 60-80% confluence and subcultured by using trypsin/EDTA.

Four separate experiments were performed to evaluate the dose-dependent effect of topiramate on keratinocyte cell growth as measured by maturity after six days of treatment. Topiramate was dissolved in DMSO to make a 100 mM stock solution. In all experiments the final concentration of DMSO in the cell incubation medium was 0.1%. Vehicle controls (0.1% DMSO) were included in each experiment. Cell growth was induced by a combination of the growth factors EGF and BPE. Topiramate had a modest inhibitory effect on cell growth under these assay conditions; however, no dose dependence was observed (R.W Johnson Pharmaceutical Research Institute Laboratory Notebook No. 12183 and 12540). The maximal response was observed at 10 micromolar, 32 ± 10% inhibition. While there was a trend toward inhibition of cell growth, this did not reach statistical significance ($p>0.05$).

The effect of topiramate on keratinocyte differentiation was measured by the expression of transglutaminase-1 protein after three days of treatment. Three separate experiments were performed. Differentiation was evaluated in both low calcium and high calcium incubation conditions. An increase in differentiation would be most readily observed under low calcium conditions whereas an inhibition of differentiation could be detected under conditions of high calcium-induced differentiation. Topiramate caused a modest increase in transglutaminase-1 protein with both conditions, indicating an enhancing effect. A follow-up study was conducted which extended the incubation time to 5 days to look for further enhancement. No additional increases in transglutaminase-1 were observed in this latter study.

The results of these studies indicate that topiramate's effects on keratinocyte function are consistent with those expected for an agent that would affect the hyperproliferative keratinocyte response associated with psoriasis; inhibition of cell growth and enhancement of differentiation.

For treating psoriasis, a compound of formula (I) may be employed at a daily dosage in the range of about 50 to 400 mg administered orally, usually in two divided doses, for an average adult human. A unit dose would contain about 25 to 200 mg of the active ingredient. Alternatively, a compound of formula (I) may be administered topically to the affected area of the skin once or twice daily at a dosage in the range of 5 to 50 mg.

To prepare the pharmaceutical compositions of this invention, one or more sulfamate compounds of formula (I) are intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral, by suppository, or parenteral. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. Thus, for liquid oral preparations, such as for example, suspensions, elixirs and solutions, suitable carriers and

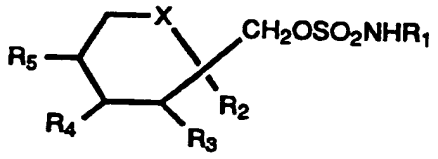
additives include water, glycols, oils, alcohols, flavoring ag nts, preservatives, coloring agents and the like; for solid oral preparations such as, for xample, powders, capsules and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar coated or enteric coated by standard techniques. Suppositories may be prepared, in which case cocoa butter could be used as the carrier. For parenterals, the carrier will usually comprise sterile water, though other ingredients, for example, for purposes such as aiding solubility or for preservation, may be included. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed.

Topiramate is currently available for oral administration in round tablets containing 25 mg, 100 mg or 200 mg of active agent. The tablets contain the following inactive ingredients: lactose hydrous, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, purified water, carnauba wax, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, synthetic iron oxide, and polysorbate 80.

The pharmaceutical compositions herein will contain, per dosage unit, e.g., tablet, capsule, powder injection, teaspoonful, suppository and the like from about 25 to about 200 mg of the active ingredient.

WHAT IS CLAIMED IS:

1. A method for treating psoriasis comprising administering to a human afflicted with such condition a therapeutically effective amount for treating such condition of a compound of the formula I:

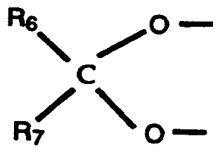


wherein

X is CH_2 or oxygen;

R_1 is hydrogen or alkyl; and

R_2, R_3, R_4 and R_5 are independently hydrogen or lower alkyl and, when X is CH_2, R_4 and R_5 may be alkene groups joined to form a benzene ring and, when X is oxygen, R_2 and R_3 and/or R_4 and R_5 together may be a methylenedioxy group of the following formula (II):



wherein

R_6 and R_7 are the same or different and are hydrogen, lower alkyl or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring.

2. The method of claim 1 wherein the compound of formula I is topiramate.

3. The method of claim 1, wherein the therapeutically effective amount is of from about 50 to 400 mg.

4. The method of claim 1, wherein the amount is of from about 25 to 200 mg.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 97/10891

A. CLASSIFICATION OF SUBJECT MATTER

A 61 K 31/35, A 61 K 31/36

According to International Patent Classification (IPC) or to both national classification and IPC 6

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A 61 K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4513006 A (MARYANOFF, B.E. et al.) 23 April 1985 (23.04.85), abstract, claims 5-9, column 1, lines 16-33, column 3, line 15 - column 5, line 19, example 3 (cited in the application). --	1-4
A	US 4792569 A (MARYANOFF, B.E. et al.) 20 December 1988 (20.12.88), abstract, claims 1,10-12, column 1, lines 20-37, column 3, line 29 - column 4, line 33. ----	1,3,4

☐ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search
14 November 1997

Date of mailing of the international search report
16.12.97

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Authorized officer
MAZZUCCO e.h.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte onal application No.
PCT/US 97/ 10891

B x I Observations where certain claims were f und unsearchable (Continuati n of item 1 f first sh et)

This International Search Report has not been established in respect f certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 1-4
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANHANG

zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

ANNEX

to the International Search Report to the International Patent Application No.

ANNEXE

au rapport de recherche international relatif à la demande de brevet international n°

PCT/US 97/10891 SAE 168598

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The Office is in no way liable for these particulars which are given merely for the purpose of information.

La présente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche international visée ci-dessus. Les renseignements fournis sont donnés à titre indicatif et n'engagent pas la responsibilité de l'Office.

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